REMARKS

I. Restriction/Election

The Examiner states Applicant's election with traverse of group I in paper number 6 is acknowledged; however the grounds are found to be non-persuasive. The requirement is still proper and therefore, made final. Accordingly, Applicants have cancelled claim 11-13, 15-25, 34, and 36-39. The cancellation of these claims does not necessitate a change in the inventorship in the application.

II. In the Drawings

The Examiner has objected to the drawings because they contain minor informalities and correction is required. Applicants have submitted herewith amendments made to Figs. 1 and 4 and are submitting a formal drawing of Fig. 10 to the official draftsperson, thus making this objection moot.

III. Claim Objection

Claim 35 is objected to because of the following informalities: it appears that the term "internalization" is misspelled as "internation". Applicants have amended claim 32 by correcting the misspelling to "internal" thus making this objection moot.

IV. Claim Rejection – 35 U.S.C. § 112

Claims 1-10, 14, 26-33, and 35 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner states that the term "increasing" is indefinite because the ordinary artisan would not know how to determine the requisite quantity necessary to be considered "increasing" and what this value is compared to. Applicants have amended claims by removing the indefiniteness and inserting the phrase "sufficiently increasing

the production of" by thus alleviating this rejection. Although Applicants have amended the claim, Applicants believe that if the claims read in light of the specification, reasonably apprise those skilled in the art of both the utilization and scope of the invention, and if the language is as precise as the subject matter permits, he can demand no more. See North Am. Vaccine, Inc. v. American Cyanamid Co., 7 F.3d 1571, 28 USPQ 2d 1333, 1339 (Fed. Cir. 1993)). Applicants believe the language of the claims read in light of the specification reasonably apprises one skilled in this relevant art the utilization of establishing a vector packaging cell line and increasing the production of viral vector titer by the claimed method.

Next, Examiner states that while Applicant may be his/her own lexicographer, a term in the claim may not be giving a meaning repugnant to the usual meaning of that term. The Examiner asserts that the term "helper virus" in claims 1-10, 14, 26-33, and 35 is used by the claim to mean "any packaging deficient vector of nucleotide sequence encoding a viral structural protein," while the accepted meaning is "these viruses such as Ad, HSV, cytomegalovirus and pseudorabies virus to serve as complete helpers to AAV." Applicants respectfully traverse this rejection. "[C]onsistent with the well-established axiom in patent law that an applicant is free to act as a lexicographer, an applicant may define a term in a manner contrary to or inconsistent with one or more of the terms ordinary meaning if that term is clearly defined in the specification." Hormone Research Found. Inc. v. Genentech Inc., 904 F.2d 1558, 15 USPQ 1039, 1043 (Fed. Cir. 1990), cert. dismissed, 499 U.S. 955 (1991). Moreover, "[a]lthough the patentee is free to define his claim terms in a manner inconsistent with their ordinary meaning, 'he must set out his uncommon definition in some manner within the patent disclosure.'" Intellicall, Inc. v. Phonometrics, Inc., 952 F.2d 1384, 1387-88, 21 USPQ 2d 1383, 1386 (Fed. Cir. 1992). Therefore, Applicants believe the usage of the term "helper virus" is not repugnant to

the usual meaning of the term because Applicants have clearly defined the term in the specification. Even if the Examiner continues to think the term is inconsistent, the Applicants are free to define the claim term as long as the uncommon definition is in some manner within the patent disclosure. On page 8 of the instant application, Applicants have clearly set out a definition for the term "helper virus." Moreover, it is believed that this definition is consistent with ordinary molecular terminology and would be readily understood by one apprised in the art. Additionally, in In re Jones, the Court held that in technical questions, standard textbook definitions are preferable to those found in general dictionaries. Genes VI by Benjamin Lewin defines a helper virus as "providing functions absent from a defective virus, enabling the later to complete the infective cycle during a mixed infection." Applicants' definition is consistent with such a definition. Besides, the claims must be read in light of the specification. Applicants have defined helper virus to read on a viral vector that has their packaging sequences removed but can provide the required packaging proteins. Applicants also take into consideration, when read in light of the specification, specialized cell lines, i.e., packaging cell lines, that can be used which contain helper virus sequences within their genomes. (See page 8 of the specification). Thus, the specification provides a sufficient definition that would enable one of ordinary skill in the art to understand the term. Applicants respectfully request Examiner to withdraw this rejection.

Likewise, the Examiner states the term "viral vector" in claims 1-10, 14, 26-33, and 35 is used by the claim to mean "any viral based vector that does not contain all structural proteins and is replication incompetent" while the accepted meaning of "a viral vector is that it contains all the elements necessary to infect and replicate in a host cell." Applicants respectfully traverse this rejection. "[C]onsistent with the well-established axiom in patent law that an applicant is free to act as a lexicographer, an applicant may define a term in a manner contrary to or inconsistent

with one or more of the terms ordinary meaning if that term is clearly defined in the specification." Hormone Research Found. Inc. v. Genentech Inc., 904 F.2d 1558, 15 USPQ 1039, 1043 (Fed. Cir. 1990), cert. dismissed, 499 U.S. 955 (1991). Moreover, "[a]lthough the patentee is free to define his claim terms in a manner inconsistent with their ordinary meaning, 'he must set out his uncommon definition in some manner within the patent disclosure.'" Intellicall, Inc. v. Phonometrics, Inc., 952 F.2d 1384, 1387-88, 21 USPQ 2d 1383, 1386 (Fed. Cir. 1992). Applicants have clearly recited a definition of the term "viral vector" in the specification. (See page 9, line 18). Moreover, it is believed that this definition is consistent with ordinary molecular terminology and would be readily understood by one apprised in the art. Additionally, Applicants respectfully would like to point out first that the Examiner fails to disclose any source where the accepted meaning of his definition comes from. Second, the Examiner fails to recite Applicant's entire definition. Note on page 9, line 22, Applicants continue to define viral vector as typically including foreign DNA that is desired to be inserted in a wholesale and usually includes and expression cassette. One of ordinary skilled in the art would know that viral vectors are retroviral vectors used as a means to introduce foreign DNA into the genome of a host cell. As a result, one having ordinary skill in the art would understand what the term viral vector means in the claim, in light of the specification, therefore Applicants respectfully request the Examiner to withdraw this rejection.

V. Claim Rejection – 35 U.S.C. § 102

Claims 1, 6-10, 14, 26, and 27 were rejected under 35 U.S.C. § 102(a) as being anticipated by Gram et al. (Journal of Hemototherapy, 1988), which discloses a MLV-derived retroviral vector that encodes two genes hGFP and Neo. The replication deficient MLV-derived retroviral vector is inserted to the PG13 packaging cell. DNA demethylation of the packaging

cell with 5-azacytidine results in an increase in the transcription and expression of the "viral vector," indicating the DNA methylation leads to the silencing of gene expression. The Examiner further states that the ability of the retroviral promoter LTR sequences to become methylated is an inherent property of the promoter and is known to result in a reduced expression from that promoter. The Examiner concludes by stating supplying a cell with a demethylating agent will result in the demethylation of all LTR promoters present in the cell and thereby resulting in increased expression from LTR promoters in the cells. Therefore the instant invention is anticipated by Gram et al. For prior art to anticipate under 35 U.S.C. § 102, every element of the claimed invention must be identically disclosed in a single reference. Corning Glass Works v. Sumitomo Electric, 9 USPQ2d, 1965 (Fed. Cir. 1989). "The exclusion of a claimed element, no matter how unsubstantial or obvious, from a prior art reference is enough to negate anticipation." Cornell v. Sears, Roebuck & Co.Cornell v. Sears, Roebuck & Co., 220 USPQ 193, 198 (Fed. Cir. 1983) (citations omitted.) The claimed invention is clearly distinguishable from Gram et al.

Gram's focus is using 5- azacytidine to eliminate the DNA methylation on vector, which involved in an inhibition mechanism of DNA methyltransferase (Juttermann, R., E. Li, and R. Jaenisch. 1994. Toxicity of 5-aza-2'-deoxycytidine to mammalian cells is mediated primarily by covalent trapping of DNA methyltransferase rather than DNA demethylation. Proc.Natl. Acad. Sci. USA. 91:11797-11801). The present invention constructs a chimeric helper virus comprised of an internal ribosome entry site along with a marker selection gene downstream of the gag pol env genes which provides for positive selection of helper virus, not inactivated by methylation (i.e., the IRES-Zeo sequence), an element not taught or disclosed by Gram et al. therefore, Gram et al. fails to anticipate the instant invention. Note on page 43 line 21, the Applicants have

compared the present invention to the 5- azacytidine treatment from Gram et al and demonstrated that the present invention is much superior than 5- azacytidine treatment from Gram et al.

The instant invention is also distinguishable from Gram et al. because Gram's focus is determining whether hGFP could function as a marker gene in a retroviral vector and to investigate the expression of genes in a retroviral vector and not with the vector titer nor decreasing the inactivation effects of DNA methylation on helper virus in viral producing cells, as in the instant application. Thus, for the aforementioned reasons, Applicants invention is distinguishable from Gram and therefore, not anticipated. Applicants respectfully request the Examiner to withdraw this rejection.

VI. Claim Rejections – 35 U.S.C. § 103

Claims 1-10, 14, 26-33, and 35 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Miller (U.S. Patent No. 5,766,945) and Gurtu et al. (BBRC 1996) in view of Gram et al. (J. of Hematotherapy, 1998). The Examiner states it would have been obvious to one of ordinary skill in the art to produce a retroviral packaging cell utilizing retroviral LTR as the promoter according to the methods described by Miller and including the efficiency of the selectable marker utilizing an internal ribosome entry site from a picornavirus as taught by Gurtu et al. The Examiner further states that providing a compound that demethylates DNA as taught by Gram et al. would allow for the most efficient transcription from the LTR promoter resulting in increased viral production in the system taught [by] Miller, Gurtu et al., and Gram et al. The Examiner concludes that one having ordinary skill in the art would have been motivated to do this order to maximize the production of recombinant viral particles obtained from the packaging system. Therefore, the instant invention is obvious over Miller and Gurtu et al. in view of Gram et al. Applicants respectfully traverse this rejection.

The PTO bears the burden of establishing a case of prima facia obviousness. In re Fine, 837 F.2d 1071, 1074 (Fed. Cir. 1988). The critical inquiry for obviousness is whether "there is something in the prior art as a whole to suggest the desirability and thus the obviousness of making the combination." Lindemann Maschinenfabrik Gmbh v. American Hoist & Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). "To establish prima facia obviousness in the claimed invention, all the claim limitation must be taught or suggested by the prior art." In re Royka, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1970).

As stated by the Examiner, the instant invention is drawn to a method of increasing a viral titer in a vector packaging cell by contacting a vector packaging cell with a viral vector and inhibiting methylation of the LTR promoter to increase the amount of helper virus in a cell. While Miller teaches the production of retroviral packaging cell lines in which the structural genes, specifically env are driven from the LTR promoter and the production of replication incompetent viral particles and the incorporation of heterologous sequences, Miller fails to teach providing a selection marker located on the same mRNA molecule through the use of an internal ribosomal entry site, as disclosed in the instant invention.

Gurtu et al. teaches the expression of two genes from the same mRNA molecule by utilizing an internal ribosome entry site from a picornavirus. The reference generally teaches that this procedure would improve the production of stable mammalian cell lines because those cells that do not express the gene of interest would be eliminated by the selection pressure of the antibiotic. Furthermore, the reference teaches the utilizing the internal ribosome entry site allows for the selected pressure provided by the antibiotic to be exerted on the entire expression cassette, which results in selecting cells expressing high levels of the protein of interest using high doses of antibiotic. However, Gurtu et al. did not anticipate that internal ribosome entry site with a

selection marker could be utilized on the elimination of DNA methylated helper virus. The Applicants discovered that the silencing of gene expression of helper virus, which consequentially decreases vector titer, is resulted from DNA methylation (Young et al. 2000. DNA methylation of helper virus increases genetic instability of retroviral vector producer cells. J. Virol 74:3177-3187; See specification, page, 31, lines11-16), and then invented a chimeric helper virus constructed with an internal ribosome entry site and a selection marker, which can be used to eliminated the silenced helper virus to boost vector titer (See specification, page 30, lines 16-20). In addition to vector production, this chimeric helper virus was also used as a scientific tool by Applicants to demonstrate the progress of DNA methylation of helper virus (See specification, page 37, line 10).

There is no suggestion in either of the references that they be combined in the manner suggested by Examiner. Absent such a suggestion, a person skilled in the art who is looking for a solution to the problem of the suppression of helper virus gene expression in a packaging cell line by DNA methylation in order to amplify the vector production would hardly be disposed on any objective bases, to consider a reference like Gurtu et al., which is not only unconcerned with packaging cells lines at all, but which shows absolutely no recognition of the problem of efficient retroviral vectors able to transduce a range of cell types, let alone any method that would solve it.

Additionally, it would not have been obvious to one of ordinary skill in the art to provide a compound that demethylates DNA as taught by Gram et al. that would allow for the most efficient transcription from the LTR promoter of helper virus resulting in increased viral production in the system taught by Miller, Gurtu et al, and Gram et al. As stated by the Examiner, Gram et al. does not teach using an internal ribosomal entry site in expressing the gene of interest or expressing the viral structural protein from the packaging cell line. Moreover,

there is no suggestion in either of the references that they be combined in the manner suggested by the Examiner. Absent such a suggestion, a person skilled in the art who is looking for a solution to the problem of using a bicistronic vector to improve the efficiency of stable cell line production as exhibit by Gurtu et al., would hardly be dispose on any objective basis to consider a reference like Gram et al., which fails to teach the use of an internal ribosomal entry site in expressing the gene of interest as exhibited by Gurtu et al., or expressing the viral structural proteins from the packaging cell lines. Therefore, claims 1-10, 14, 26-33, and 35 are patentably distinct from the combination of Miller and Gurtu et al. in view of Gram et al. Applicants therefore respectfully request the Examiner to withdraw this rejection.

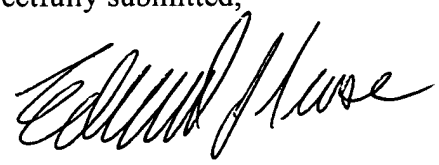
VII. Conclusion

No fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Reconsideration and allowance is respectfully requested.

Respectfully submitted,



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AMENDMENT — VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification

Please amend specification as follows:

Page 21, line 27, delete "http://www.standford.edu/group/nolan/nl-phoenix.html)" and insert --) -- after the word line.

In the Claims

Please amend claims 1, 2, 9, 26, and 35 as follows:

1. (Amended)

A method for establishing a vector packaging cell line and sufficiently increasing the production of viral vector titer in [a] the vector packaging cell comprising:

[contacting] introducing a [vector packaging] helper virus into a cell to establish a packaging cell line, said helper virus [with a viral vector, said viral vector] comprising a [viral packaging signal sequence] genome sequence viral structural proteins in combination with an internal ribosome entry site with a selection marker and a nucleotide sequence, the presence of which [is desired in] enables a host cell to be [, said packaging cell] capable of expressing [structural] an introduced viral components to form a [so that said] viral [vector] particle so that said viral vector may be assembled [to form an infectious] into the viral particle to form an infectious viral particle; and

increasing the vector production by inhibiting the presence of [5' methylated] DNA methylation of helper virus in said cell.

2. (Amended)

The method of claim 1 wherein said step of inhibiting the presence of DNA methylation comprises:

positively selecting helper virus which is functional.

9. (Amended)

The method of claim 1 wherein said step of decreasing inactive helper virus comprises the step of:

inhibiting [~~methylation of helper virus~~] the presence of DNA methylation of helper virus in a cell.

26. (Amended)

A method for [increasing viral titer produced by] establishing a vector packaging cell and increasing the production of viral vector titer upon transfection with a viral vector comprising:

decreasing the amount of inactive helper virus present in said vector packaging cell by providing for the elimination of or prevention of methylated helper virus.

35. (Amended)

The method of claim 27 wherein said inhibiting of methylation is accomplished by a step selected from the group consisting of:

ligation of an [internation] internal ribosome entry site with a selection marker so that drug selection would ensure promoter function of a helper virus.